PCT/GB 00/01857

15 MAY 2000

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

RECD 28 JUN 2000
PCT

GB00/1857

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

4

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed R. Mahoney

Dated 25th May 2000

For official use

THE PATENT OFFICE
A
14 MAY 1999
LONDON

14 MAY 1999

Your reference 230P80673X

9911346.6

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071–438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

Warning
After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked:

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: Treatment of Cancers

❷ Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: Pharma Mar, S.A.

Country *(and State of incorporation, if appropriate)*: Spain

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: Calle de la Calera, 3
Polígono Industrial de Tres Cantos
28760 Tres Cantos, Madrid
Spain

UK postcode *(if applicable)*

Country

ADP number *(if known)*

438114 1002

2d, 2e **2f:** *If there are further applicants please provide details on a separate sheet of paper.*

☐ **Second applicant** ***(if any)***

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases**, please give the following details:

Address

UK postcode *(if applicable)*

Country

ADP number *(if known)*

❸ *An address for service in the United Kingdom must be supplied*

Please mark correct box

❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] → ***go to 3b***

↓

please give details below

Agent's name: Marks & Clerk

Agent's address: 57-60 Lincoln's Inn Fields
LONDON
WC2A 3LS.

Postcode

Agent's ADP number: 18001 ✓

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number *(if available)*

ADP number *(if known)*

❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* 230P80673X

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ → ***go to 6***

↓

please give details below

☐ number of earlier application or patent number

☐ filing date

(day month year)

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ *The answer must be 'No' if: any applicant is not an inventor, there is an inventor who is not an applicant, **or** any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐ No ☒ ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	—		
Claim(s)	—	Description	3
Abstract	—	Drawing(s)	—

DBK

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	—
Translation(s) of Priority documents *(please state how many)*	—
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	—
Patents Form 9/77 – Preliminary Examination/Search	—
Patents Form 10/77 – Request for Substantive Examination	—

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

❾ Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡ Signed Marks & Clerk Date 14 (day) - 5 (month) - 99 (year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

❑ ***The Comptroller***
The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

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The Patent Office
25 Southampton Buildings
London
WC2A 1AY

Document #: 378951

Treatment of Cancers

The present invention relates to the treatment of cancers.

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

We have now found that ecteinascidin 743 has exceptional activity in the treatment of sarcomas and mesotheliomas. A sarcoma is a cancer arising from connective tissue such as muscle or bone. A mesothelioma is a tumour of the mesothelium of the pleura, pericardium or peritoneum.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by a sarcoma or mesothelioma which comprises administering to the affected individual a therapeutically effective amount of ecteinascidin 743, or a pharmaceutical composition thereof. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient ecteinascidin 743, as well as the processes for its preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. Intravenous delivery may be carried out over any suitable time period, such

as 12 to 24 hours or even longer if required, at suitable intervals of say 2 to 4 weeks. Pharmaceutical compositions containing ecteinascidin 743 may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of ecteinascidin 743 of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin , paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics; and

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

The present invention also extends to the compounds for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

Example

A group of 22 sarcoma patients, including soft tissue sarcomas (fibrosarcomas, leyomiosarcomas, mesotheliomas, etc.) and bone sarcomas (osteosarcomas) have been treated at the maximum tolerated dose (MTD) and recommended dose (RD) during phase 1 trials. Patients' characteristics include 10 men and 12 women, median age 52 (17-68) years, all pre-treated with anthracyclines or alkylators with 1 to 4 previous chemotherapy treatments, median performance status (PS) 1 (0-1) (ECOG), median number of metastatic sites 2 (1 to 7) were treated with ET-743. 11 patients were treated at a dose of 1500 mcg/m2 or over during a 24 hour infusion (9 patients into a clinical trial and 2 patients as compassionate use). One patient was treated at 1500 mcg/m2 in the 3 hour infusion study; 3 patients in the daily times five study (1 hour infusion x 5 days) at doses over 1625 mcg/m2 and 7 patients in the 72 hour continuous infusion at doses over 1050 mcg/m2.

In this group of patients the following responses have been observed: six partial responses (2 osteosarcomas, 2 leiomyosarcomas, 1 fibrosarcoma, 1 mesothelioma) 3 of which lasting over 4 months, one minor response and 4 stabilisations (WHO criteria).

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23/77 Rec'd 15-5-2000

Marks + Clerk